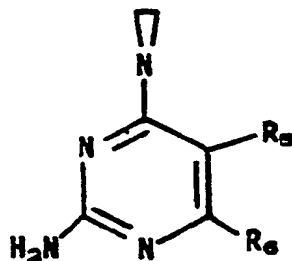


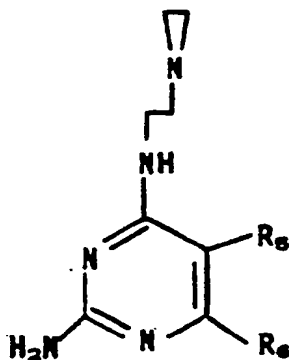


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁴ : C07D 239/42, 403/04, 403/12 A61K 31/505	A1	(11) International Publication Number: WO 86/ 04583 (43) International Publication Date: 14 August 1986 (14.08.86)
(21) International Application Number: PCT/US86/00074 (22) International Filing Date: 23 January 1986 (23.01.86) (31) Priority Application Number: 698,309 (32) Priority Date: 5 February 1985 (05.02.85) (33) Priority Country: US (60) Parent Application or Grant (63) Related by Continuation US 698,309 (CIP) Filed on 5 February 1985 (05.02.85) (71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; Kalamazoo, MI 49001 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : SKULNICK, Har- vey, I. [US/US]; 1745 Old Deer Run, Kalamazoo, MI 49009 (US). WIERENGA, Wendell [US/US]; 6219 Countrywood Court, Kalamazoo, MI 49009 (US). (74) Agent: JAMESON, William, G.; Patent Law Depart- ment, The Upjohn Company, Kalamazoo, MI 49001 (US). (81) Designated States: BE (European patent), CH (Euro- pean patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: 4-SUBSTITUTED-6-ARYL PYRIMIDINE COMPOUNDS

(IA)



(IB)

(57) Abstract

Synthesis and anti-neoplastic use of 4-aziridyl-5-substituted/unsubstituted 6-aryl-pyrimidine compounds of formula (IA) as well as N'-(2-(1-aziridyl)ethyl)-6-aryl-2,4-pyrimidinediamines of formula (IB) and 4-chloro or bromo-5-substituted/unsubstituted -6-aryl-pyrimidines.

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4-SUBSTITUTED-6-ARYL PYRIMIDINE COMPOUNDS

BACKGROUND OF THE INVENTION

Traditional treatments of cancer have utilized surgery, irradiation
5 and chemotherapy. New classes of compounds are developed for use as
chemotherapeutic agents. 5-Fluorouracil is a well known and widely
used antineoplastic agent. Wierenga et al. disclose the use of 2-
amino-6-aryl-5-substituted-4-pyrimidinols (pyrimidines) as interferon
inducers, antiviral agents and for treatment of cancer in Belgium
10 Patent No. 882,315 and Great Britain Patent No. 2,048,250.

The preparation of 4-chloro-6-phenyl-2-pyrimidinamine by the
chlorination of 2-amino-6-phenyl-4(3H)-pyrimidinone with phosphorus
oxychloride is described by Wierenga et al in Synthesis of 2-amino-6-
phenyl-4(3H)-pyrimidinone-1-oxide, Heterocycles, 16(4), 563-71 (1981)
15 and Chemical Abstracts 95 (5):43025r.

4-Chloro-6-phenyl-2-pyrimidinamine is also disclosed in Heterocycles,
8, 299-305 (1977), Chemical Abstracts 88(15):105255g and Izv. Akad. Nauk
SSSR, Ser. Khim., 10, 2173-6 (1971), Chemical Abstracts 76(9):45330t.

There are a number of examples of aziridine-containing anticancer
20 agents, including triethylenemelamine, triethylenethiophosphoramide
(thio-TEPA), aziridylbenzoquinone, mitomycins and 1-(2,3,5-tribenzoyl-
β-1)-ribofuranosyl)-4-aziridyl-2-pyrimidinone. See W.B. Pratt and
R.W. Ruddon, The Anti-Cancer Drugs, Oxford Univ. Press, N.Y., 1979 and
S.K. Carter, et al (ed.), Recent Results in Cancer Research, Springer-
25 Verlag, Berlin, 1977 for a review.

BRIEF DESCRIPTION OF THE INVENTION

This application relates to 4-substituted-5-substituted/unsubstituted-
6-aryl-pyrimidine compounds represented by Formula I, wherein R₄ is
chloro, bromo, aziridyl or 2-(1-aziridyl)ethylamino and R₅ and R₆ are
30 as defined below, and the use thereof to treat an animal or human
hosting a neoplastic disease.

DETAILED DESCRIPTION OF THE INVENTION

The 4-substituted-6-aryl-pyrimidine compounds represented by Formula
I, including the 4-aziridyl-6-aryl-pyrimidine compounds represented by
35 Formula IA and the N'-[2-(1-aziridyl)ethyl]-6-aryl-2,4-pyrimidinediamine

SUBSTITUTE SHEET

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compounds represented by Formula IB wherein R₅ is hydrogen, fluoro, chloro, bromo or iodo and R₆ is a member selected from the group consisting of

- a) phenyl,
- 5 b) a monosubstituted phenyl of Formula A wherein one of the Groups X, X₁, X₂, X₃ or X₄ is not hydrogen and is fluoro, chloro, bromo, iodo, alkyl of from 1 to 5 carbon atoms, inclusive, including isomeric forms, alkoxy of from 1 to 5 carbon atoms, inclusive, including isomeric forms, nitro or
10 dialkylamino of from 1 to 3 carbon atoms, inclusive, including isomeric forms, and
- c) a disubstituted phenyl of Formula A wherein any two of X, X₁, X₂, X₃ and X₄ are not hydrogen and are the same or different and are fluoro, chloro, bromo, iodo, alkyl of from 1 to 5
15 carbon atoms, inclusive, including isomeric forms, alkoxy of from 1 to 5 carbon atoms, inclusive, including isomeric forms, nitro or dialkylamino of from 1 to 3 carbon atoms, inclusive, including isomeric forms, and

are prepared from 6-aryl-pyrimidinol compounds of Formula II by the
20 procedures illustrated in Chart A.

The 6-aryl-pyrimidinol compounds are, however, tautomeric and can therefore also be drawn and/or named as isocytosines (Formula IIB), for example 2-amino-5-bromo-6-phenyl-4-pyrimidinol can also be named as 5-bromo-6-phenyl-isocytosine.

25 The 6-aryl-pyrimidinol compounds of Formula II can be obtained by the methods disclosed in Belgium Patent No. 882,315 or Great Britain Patent No. 2,048,250.

30 The starting 6-aryl-pyrimidinol (Formula II) is reacted with phosphorous oxychloride or phosphorous oxybromide, in the presence of heat to give the compound of Formula III where Z is chloro or bromo.

The compounds of Formula III, preferably where Z is chloro, is reacted with aziridine in the presence of an aprotic base, for example triethylamine, and carried out at 0° to 50°.

35 If the compounds of Formula III are unsubstituted at the 5-position, the compounds of Formula IA or IB can be halogenated, if desired, by well known art methods. See, Preparation III or IV and Chart B.

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DEFINITIONS

The definitions and explanations below are for the terms as used throughout the entire patent application including both the specification and the claims.

- 5 - All temperatures are in degree Centigrade.
 - TLC refers to thin-layer chromatography.
 - THF refers to tetrahydrofuran.
 - THP refers to tetrahydropyranyl.
 - DMSO refers to dimethylsulfoxide.
- 10 - Skellysolve B refers to an isomeric mixture of hexanes.
 - DMA refers to dimethylacetamide.
 - NBS refers to N-bromosuccinimide.
 - NCS refers to N-chlorosuccinimide.
 - TEA refers to triethylamine.
- 15 - Saline refers to an aqueous saturated sodium chloride solution.
 - IR refers to infrared spectroscopy.
 - CMR refers to ¹³C magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.
 - NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane.
- 20 - TMS refers to trimethylsilyl.
 - MS refers to mass spectrometry expressed as m/e or mass/change unit.
 - Ether refers to diethyl ether.
- 25 - Alcohol refers to ethyl alcohol.
 - Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological-toxicological point of view and to the manufacturing pharmaceutical chemist from a physical-chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.
- 30 - When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).
 - When the term "alkyl of 1 through 5 carbon atoms" is used, it means and includes isomers thereof where such exist.
- 35 The following Preparations and Examples are to be construed as merely illustrative of compounds of Formula I and means of preparing

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said compounds, and not limitative of the remainder of the disclosure.

Example 1 Synthesis of 4-chloro-6-phenyl-2-pyrimidinamine; 2-amino-4-chloro-6-phenylpyrimidine

To 10.0 g (53 mM) of 6-phenylisocytosine is added 80 ml of phosphorus
5 oxychloride. The mixture is heated to reflux, and refluxed until
solution is complete (about 30 minutes). The solution is then cooled
and evaporated to dryness under vacuum at 45°C. The resulting oil is
poured into 300 ml of ice water, with vigorous stirring, and the remaining
oil washed into the aqueous mixture with additional 100 ml of water.
10 The entire aqueous mixture is neutralized to pH 8 with concentrated
ammonium hydroxide, filtered, and solids washed well with water until
water wash is neutral. Dry at 60° in a vacuum oven to yield 9.2 g of
4-chloro-6-phenyl-2-pyrimidinamine.

Example 2 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine; 2-amino-4-(1-
15 aziridyl)-6-phenylpyrimidine

To 10.0 g (48.7 mM) of 4-chloro-6-phenyl-2-pyrimidinamine is added
a solution of 10.25 ml of triethylamine (73 mM) in 50.0 ml of aziridine
(965 mM). The mixture is stirred at 20° for 24 hours and evaporated,
under vacuum to dryness (the distillate is collected in a trap that is
20 cooled with a dry-ice/acetone bath, and then carefully discarded). The
residue is dissolved in a minimum amount of methanol and poured into
1500 ml of ethyl acetate. The solids are filtered and the organic
solution evaporated to dryness under vacuum. The residue is dissolved
in 50.0 ml of ethyl acetate, placed on top of 500 g silica gel and
25 eluted with ethyl acetate taking 50.0 ml fractions. The desired fractions
are pooled (Rf 0.5 in ethyl acetate) and evaporated to dryness to yield
2.3 g of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine. m.p. 146-147°.

Calculated for C₁₂H₁₂N₄: C, 67.90; H, 5.70; N, 26.40.

Found: C, 67.72; H, 5.85; N, 26.29.

30 ¹H NMR (d₆ acetone): 8.16-7.96 7.63-7.36, 6.78, 2.26.

Example 3 4-(1-aziridyl)-5-bromo-6-phenyl-2-pyrimidinamine; 2-
amino-4-(1-aziridyl)-5-bromo-6-phenylpyrimidine

To 106 mg (0.5 mM) of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine is
added 2 ml of dry N,N-dimethylformamide followed by 97 mg of N-bromo-
35 succinimide. The reaction mixture is held at 20° for 96 hours. The
mixture is evaporated to dryness under high vacuum and two ml's of 95%

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ethanol are added. The mixture is held at 20° for 1 hr, filtered, and the crystals washed with 95% ethanol to yield 30 mg of 4-(1-aziridyl)-5-bromo-6-phenyl-2-pyrimidinamine.

m.p. 160.5-161°.

5 Calculated for $C_{12}H_{11}BrN_4$: C, 49.50; H, 3.81; N, 19.14; Br, 27.45.

Found: C, 49.60; H, 4.08; N, 18.98; Br, 27.53.

H^1 NMR (D_6 MSO): 7.65-7.3, 6.70, 2.35.

Example 4

Part I

10 Synthesis of 5-fluoro-6-phenylisocytosine

A. Preparation of ethyl- α -fluoro-benzoyl-acetate.

To 8.88 g NaH/oil is added 100 ml (diethylether-washes) and decanted twice. An additional 100 ml of diethylether is added. With stirring, 20 g (188 mM) of ethylfluoroacetate is added dropwise, and when the
15 addition is complete, the reaction is allowed to stir at ambient room temperature for 45 minutes.

Cooled to -50° and add 13.39 g (95 mM) benzoyl chloride, slowly, and with careful temperature control. When addition is complete the ice bath is removed and the reaction allowed to stir for an additional
20 45 minutes. The reaction mixture is poured into 400 ml of ice-cold ice/sulfuric acid, 100 ml diethylether added and the organic layer washed once with water, twice with saturated sodium bicarbonate, twice with water and dried over magnesium sulfate (anhydrous). Filtered, evaporated and distilled the residue at 3.5 mm gives 3.3 g (16%) of the
25 fluoro β -keto ester, b.p. 94-100° at 3.5 mm.

B. Synthesis of title compound.

To 575 mg (3.2 mM) of guanidine carbonate is added 40 ml of absolute ethanol + 2 ml of toluene. Heated to reflux and azeotrop off 13 ml of solvent, cooled, and add 1.35 g (4 mM) of ethyl- α -fluoro-benzyl-acetate.
30 Allow to heat at reflux, with continuous stirring, for 18 hours.

Add 25.0 ml of water, cooled, and neutralized by the addition of carbon dioxide chips. The solids are filtered and washed well with water followed by diethylether. The crude title compound is recrystallized from 95% ethanol to yield 260 mg mp 276-8° of 2-amino-5-fluoro-6-phenyl-
35 4(3H)-pyrimidinone; 5-fluoro-6-phenylisocytosine.

Part II

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Synthesis of 4-chloro-5-fluoro-6-phenyl-2-pyrimidinamine; 2-amino-4-chloro-5-fluoro-6-phenylpyrimidine

To 200 mg of 5-fluoro-6-phenylisocytosine is added 12 ml of phosphorus oxychloride. The mixture is heated to reflux, and refluxed for ten minutes. The solution is then cooled and evaporated to dryness under vacuum, titrated with ice-water, neutralized with concentrated ammonium hydroxide added dropwise until the solution remains basic (pH-9) and stirred for a period of 30 minutes, the solids filtered, washed with water, and dried at 50°C in a vacuum oven to yield 56 mg of 4-chloro-5-fluoro-6-phenyl-2-pyrimidinamine.

Calculated for $C_{10}H_7ClFN_3$: C, 53.70; H, 3.15; N, 18.79.

Found: C, 50.77; H, 3.63; N, 18.68.

Example 5

Synthesis of N'-[2-(1-aziridyl)ethyl]-5-fluoro-6-phenyl-2,4-pyrimidinediamine.

To 50 mg (.224 mM) of 4-chloro-5-fluoro-6-phenyl-2-pyrimidine is added 4.0 ml of aziridine and 1.01 ml of triethylamine. The reaction mixture is stirred at ambient temperature for 48 hrs. The solution is evaporated to dryness under high vacuum at 20°, and the residue is dissolved in a minimal amount of ethyl acetate and chromatographed over 20 g of silica gel using 15% isopropanol/ $CHCl_3$ as eluent. A fraction containing material with a TLC of 0.35 (15% MeOH/ $CHCl_3$) is collected and evaporated to dryness to yield 18.0 mg of N'-[2-(1-aziridyl)ethyl]-5-fluoro-6-phenyl-2,4-pyrimidinediamine.

GC/MS (2'-1% Sf 30; 120° → 250° @ 15°/minute)

m/e at 273; M-55

High resolution mass spec MW calculated: 273.1389

Found: 273.1385

1H -NMR ($CDCl_3$): δ 8.5-7.80 and 7.50-7.30; 5.70-5.50; 4.78; 3.65; 2.48; 1.90-1.7. 5 and 1.30-1.10.

Example 6

Synthesis of 5-bromo-4-chloro-6-phenyl-2-pyrimidinamine; 2-amino-5-bromo-4-chloro-6-phenylpyrimidine

To 1.5 g (7.3 mM) of 4-chloro-6-phenyl-2-pyrimidinamine is added 75 ml of glacial acetic acid. This mixture is stirred to dissolve and 0.44 ml of bromine is added. The reaction is stirred at ambient

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temperature for 24 hours. The solution is evaporated to dryness under vacuum to yield 1.75 g of 5-bromo-4-chloro-6-phenyl-2-pyrimidinamine.

Calculated for $C_{10}H_7BrClN_3$: C, 42.20; H, 2.48; N, 14.77; Br, 28.10; Cl, 12.46.

5 Found: C, 42.09; H, 2.59; N, 14.68; Br, 29.90; Cl, 11.05.

NMR H^1 - 7.53.

Example 7

Synthesis of 4,5-dichloro-6-phenyl-2-pyrimidinamine

10 To 1.5 g (7.3 mM) of 4-chloro-6-phenyl-2-pyrimidinamine is added 40 ml of glacial acetic acid and 1.05 g of N-chlorosuccinimide. The reaction is stirred at ambient temperature ($-20^{\circ}C$) for 18 hours. The reaction mixture is evaporated to dryness, dissolved in acetone and 10.0 g of silica gel added and the mixture evaporated to a powder under

15 vacuum. The powder is chromatographed on 50 g silica gel and eluted with 35% ethyl acetate/hexane. A fraction containing material with a TLC r.f. of 0.7 35% ethylacetate/hexane is collected and evaporated to dryness, recrystallized from acetone/Skellysolve B (1:10), evaporated to dryness(?) to yield 0.90 g of 4,5-dichloro-6-phenyl-2-pyrimidinamine.

20 Calculated for $C_{10}H_7Cl_2N_3$: C, 50.03; H, 2.93; N, 17.50; Cl, 29.54.
Found: C, 50.19; H, 2.98; N, 17.78; Cl, 29.50.

H^1 -NMR: 7.83-7.36; 5.8-5.55.

Example 8

Synthesis of 4-chloro-5-iodo-6-phenyl-2-pyrimidinamine; 2-amino-4-chloro-5-iodo-6-phenylpyrimidine

25

To 3.12 g (10mM) of 5-iodo-6-phenylisocytosine is added 30 ml of phosphorus oxychloride. The mixture is heated to dissolve, cooled to room temperature and evaporated to dryness under vacuum at $45^{\circ}C$. The resulting oil is added to 200 ml of water and the mixture neutralized

30 by the addition of concentrated ammonium hydroxide. The solids are filtered, washed with water and dried at $50^{\circ}C$ in a vacuum oven for 18 hours, and then dissolved in acetone, filtered and 10.0 g of silica gel added and the mixture evaporated to a powder under a vacuum. The powder is chromatographed on 50 g silica gel and eluted with 35% ethyl

35 acetate/hexane to yield, after crystallization from acetone/Skellysolve B (1:15), 0.6 g of 4-chloro-5-iodo-6-phenyl-2-pyrimidinamine.

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Calculated for $C_{10}H_7IClN_3$: C, 36.25; H, 2.12; N, 12.68; Cl, 10.70;
I, 38.31.
Found: C, 36.38; H, 2.17; N, 12.91; Cl, 10.91;
I, 38.11.

5

ANTILEUKEMIA ACTIVITY

4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, 4-(1-aziridyl)-5-bromo-
6-phenyl-2-pyrimidinamine, N'-[2(1-aziridyl)ethyl]-5-fluoro-6-phenyl-
2,4-pyrimidinediamine, 4-chloro-5-fluoro-6-phenyl-2-pyrimidinamine,
4,5-dichloro-6-phenyl- α -pyrimidinamine, 4-chloro-5-iodo-6-phenyl-2-
10 pyrimidinamine, 5-bromo-4-chloro-6-phenyl-2-pyrimidinamine and 4-chloro-
6-phenyl-2-pyrimidinamine, have been shown to inhibit the growth of L-
1210 mouse leukemia cells in vitro as shown in Table I. The L-1210
tube dilution assay is described in detail in a publication by L.H. Li,
et al, Cancer Research 39:4816 (1979). ID₅₀ and ID₉₀ refer to the
15 concentration of compound needed to inhibit cell growth by 50 and 90
percent, respectively.

4-(1-aziridyl)-6-phenyl-2-pyrimidinamine also demonstrated activity
in vivo against P388 and L-1210 leukemias in mice but no in vivo activity
in mice against B-16 melanoma. The P-388 mouse leukemia test is described
20 in detail in a publication by G.L. Neil, et al, Cancer Treatment Reports
63, 1971-1978 (1979). The results of in vivo testing using different
dosage schedules is shown in Table II.

The compounds of the subject invention (Formula I) or the pharmaco-
logically acceptable acid addition salts thereof when R₄ is chloro or
25 bromo, in association with a pharmaceutical carrier can be used to
treat animals or humans hosting a neoplastic disease, for example,
acute adenocarcinoma of lung, neuroblastoma, small cell carcinoma of
lung, breast carcinoma, lymphomas, leukemias, colon carcinoma, ovarian
carcinoma, bladder carcinoma, and the like. Suitable pharmacologically
30 acceptable acid addition salts are, for example, the hydrochloride,
sulfate, phosphate, nitrate, and the like. These salts can be used in
the same manner as the base compounds.

The dosage administered will be dependent upon the identity of the
neoplastic disease, the type of host involved, its age, health, weight,
35 kind of concurrent treatment, if any, frequency of treatment and
therapeutic ratio.

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Illustratively, dosage levels of the administered active ingredients can be: intravenously or interaperitoneally at 10 to about 100 mg/kg/day intraperitoneally or orally at 10 to about 1000 mg/kg/day.

For humans, illustratively, dosage levels of the administered
5 active ingredient can be: orally at 10 to about 1000 mg/kg/day, or preferably intravenously at 1 to about 100 mg/kg/day; the foregoing dose to be administered in one day. The dose can be readministered at daily intervals for 3-10 days for a course of therapy. Courses of therapy can be repeated at intervals, for example, every 4 weeks.

10 Expressed in terms of concentration, an active ingredient can be present in the compositions of the present invention in a concentration of from about 0.1 to about 90 percent w/w of the composition; preferably about 1 to about 20 percent w/w of the composition; and for parenteral use in a concentration of from about 0.5 to about 50 percent w/v of the
15 composition and preferably from about 5 to about 20 percent w/v.

The compositions of the present invention are preferably presented for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions
20 or suspensions, and oral solutions or suspensions and the like, containing suitable quantities of an active ingredient.

For oral administration either solid or fluid unit dosage forms can be prepared.

Powders are prepared quite simply by comminuting the active ingredient
25 to a suitably fine size and mixing with a similarly comminuted lactose or starch. Advantageously, a sweetening agent or sugar is present as well as a flavoring gel.

Capsules are produced by preparing a powder mixture as hereinbefore described and filling into formed gelatin sheaths. Advantageously, as
30 an adjuvant to the filling operation, a lubricant such as talc, magnesium stearate, calcium stearate and the like is added to the powder mixture before the filling operation.

Soft gelatin capsules are prepared by machine encapsulation of a slurry of active ingredients with an acceptable vegetable oil, light
35 liquid petrolatum or other inert oil or triglyceride.

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Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and pressing into tablets. The powder mixture is prepared by mixing an active ingredient, suitably comminuted, with a diluent or base such as starch, lactose, kaolin, dicalcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as corn syrup, gelatin solution, methylcellulose solution or acacia mucilage and forcing through a screen. As an alternative to granulating, the powder mixture can be slugged, i.e., run through the tablet machine and the resulting imperfectly formed tablets broken into pieces (slugs). The slugs can be lubricated to prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearic salt, talc or mineral oil. The lubricated mixture is then compressed into tablets.

Advantageously the tablet can be provided with a protective coating consisting of a sealing coat or enteric coat of shellac, coating of sugar and methylcellulose and a polish coating of carnauba wax.

Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared wherein each teaspoonful of composition contains a predetermined amount of active ingredient for administration. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic vehicle with suitable sweeteners together with a flavoring agent. Suspensions can be prepared of the insoluble forms with a suitable vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

For parenteral administration, fluid unit dosage forms are prepared utilizing an active ingredient and a sterile vehicle, water being preferred. The active ingredient, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the water-soluble active ingredient can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. Parenteral suspensions are prepared in substantially the same manner except that an active ingredient is suspended in the vehicle

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instead of being dissolved and sterilization cannot be accomplished by filtration. The active ingredient can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate
5 uniform distribution of the active ingredient.

The active ingredients can also be admixed in animal feed. The active ingredients can conveniently be prepared in the form of a food premix. The food premix can comprise an active ingredient in admixture with an edible pharmaceutical diluent such as starch, oatmeal, flour,
10 calcium carbonate, talc, dried fish meal and the like nontoxic, orally acceptable pharmaceutical diluents. The prepared premix is then conveniently added to the regular feed.

The term "unit dosage form" as used in the specification and claims refers to physically discrete units suitable as unitary dosages
15 for human and animal subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and are directly dependent on (a) the unique
20 characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitation inherent in the art of compounding such an active material for therapeutic use in humans, as disclosed in this specification, these being features of the present invention. Examples of suitable unit dosage forms in accord with this
25 invention are tablets, capsules, troches, suppositories, powder packets, wafers, chachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

The active ingredients to be employed can be easily prepared in
30 unit dosage form with the employment of pharmaceutical materials which themselves are available in the art and can be prepared by established procedures. The following preparations are illustrative of the preparation of the unit dosage forms of the present invention, but are not intended to be limiting.

35 Example I Hard-Gelatin Capsules

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One thousand two-piece gelatin capsules for oral use, each capsule containing 100 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, are prepared from the following types and amounts of ingredients:

	4-(1-aziridyl)-6-phenyl-2-pyrimidinamine,	100 gm
5	micronized	
	Lactose	100 mg
	Corn starch	20 gm
	Talc	20 gm
	Magnesium stearate	2 gm

10 The 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, finely divided by means of an air micronizer, is added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

The foregoing capsules are useful for treating lung cancer by the oral administration of one or two capsules one to four times a day.

15 Using the procedure above, capsules are similarly prepared containing 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine in 50, 250 mg and 500 mg amounts by substituting 50 gm, 250 gm and 500 gm of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine for the 100 gm used above.

Example II Soft Gelatin Capsules

20 One-piece soft gelatin capsules for oral use, each containing 250 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine finely divided by means of an air micronizer, are prepared by first suspending the compound in 0.5 ml of corn oil to render the material capsulatable and then capsulating in the above manner.

25 The foregoing capsules are useful for treating lung cancer by the oral administration of one or two capsules one to four times a day.

Example III Tablets

30 One thousand tablets, each containing 500 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, are prepared from the following types and amounts of ingredients:

	4-(1-aziridyl)-6-phenyl-2-pyrimidinamine,	500 gm
	micronized	
	Lactose	75 gm
	Corn Starch	50 gm
35	Magnesium stearate	4 gm
	Light liquid petrolatum	5 gm

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The 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, finely divided by means of an air micronizer, is added to the other ingredients and then thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then
5 compressed into tablets, each tablet containing 500 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine.

The foregoing tablets are useful for treating lung cancer by the oral administration of one or two tablets one to four times a day.

Using the procedure above, tablets are similarly prepared containing
10 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine in 250 mg and 100 mg amounts by substituting 250 mg and 100 gm of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine for the 500 gm used above.

Example IV Oral Suspension

One thousand ml of an aqueous suspension for oral use, containing
15 in each teaspoonful (5 ml) dose, 500 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, is prepared from the following types and amounts of ingredients:

	4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, micronized	100 gm
20	Citric acid	2 gm
	Benzoic acid	1 gm
	Sucrose	700 gm
	Tragacanth	5 gm
	Lemon oil	2 gm
25	Deionized water, q.s.	1,000 ml

The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, finely divided by means of an air micronizer, is stirred into the syrup until uniformly distributed.
30 Sufficient water is added to make 1,000 ml.

The composition so prepared is useful for treating leukemia at a dose of one tablespoonful (15 ml) three times a day.

Example V

A sterile aqueous suspension for parenteral injection, containing
35 in one mg 300 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, is prepared from the following types and amounts of ingredients:

-14-

	4-(1-aziridyl)-6-phenyl-2-pyrimidinamine,	
	micronized	300 gm
	Polysorbate 80	500 gm
5	Methylparaben	2.5 gm
	Propylparaben	0.17 gm
	Water for injection, q.s.	1,000 gm

All the ingredients except the 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine are dissolved in the water and the solution sterilized by filtration. To the sterile solution is added the sterilized 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, finely divided by means of an air micronizer, and the final suspension is filled into sterile vials and the vials sealed.

The composition so prepared is useful for treating adenocarcinoma at a dose of one milliliter (1 M) three times a day.

Example VI Hard Gelatin Capsules

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 100 mg of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine, are prepared from 100 gm of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine.

The 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine is finely divided by means of an air micronizer and encapsulated in the usual manner.

The foregoing capsules are useful for preventing or treating metastasis following mastectomy by the oral administration of one or two capsules one to four times a day.

Using the procedure above, capsules are similarly prepared containing 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine in 50 mg, 250 mg and 500 mg amounts by substituting 50 gm, 250 gm and 500 gm of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine for the 100 gm used above.

Example VII

Following the procedure of the preceding Examples 1 through 6, inclusive, compositions are prepared substituting equivalent amounts of the pharmaceutically acceptable acid addition salts of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine for the free base of the examples.

The antibacterial spectrum of 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine was determined in an in vitro disk plate assay. The assay procedure is as follows:

-15-

A solution of 4-(1-aziridinyl)-6-phenyl-2-pyrimidinamine was prepared at 1 mg/ml in distilled water. Paper assay disks (1/2 inch) were dripped into the solution and spotted on seeded agar trays. The zones were read after 18 hours incubation and are reported in Table III.

5 In addition, the antibacterial spectrum of 4-chloro-6-phenyl-2-pyrimidinamine was determined in the above-identified in vitro disk plate assay and exhibited a zone of inhibition (20 mm) against Proteus vulgaris. No other antibacterial activity against the test organisms was observed.

10 Thus, these compounds are also useful to control the proliferation of susceptible microbes in various environments using standard microbiological techniques. Such environments include laboratory benches in a microbiological laboratory which can be cleansed with a formulation of these compounds.

15 A formulation of 4-(1-aziridinyl)-6-phenyl-2-pyrimidinamine can be used to cleanse food processing equipment and/or utensils contaminated by Streptococcus pyogenes. It is contemplated that formulations of other compounds of Formula IA can also be used in a like manner.

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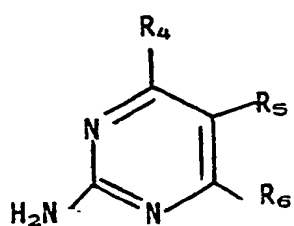
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-16-

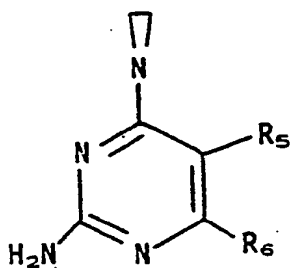
FORMULA

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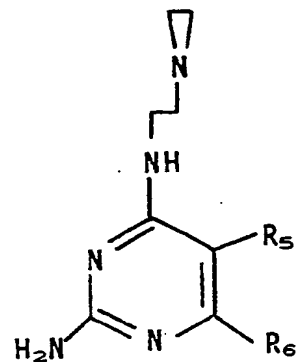
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I



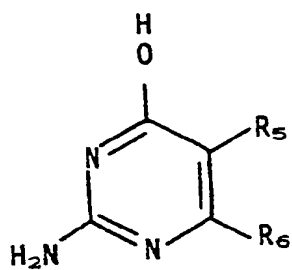
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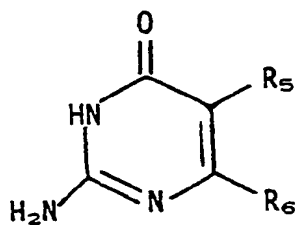
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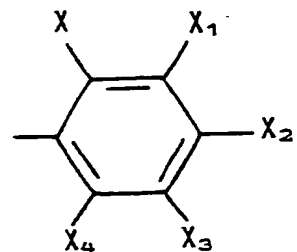
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IIB

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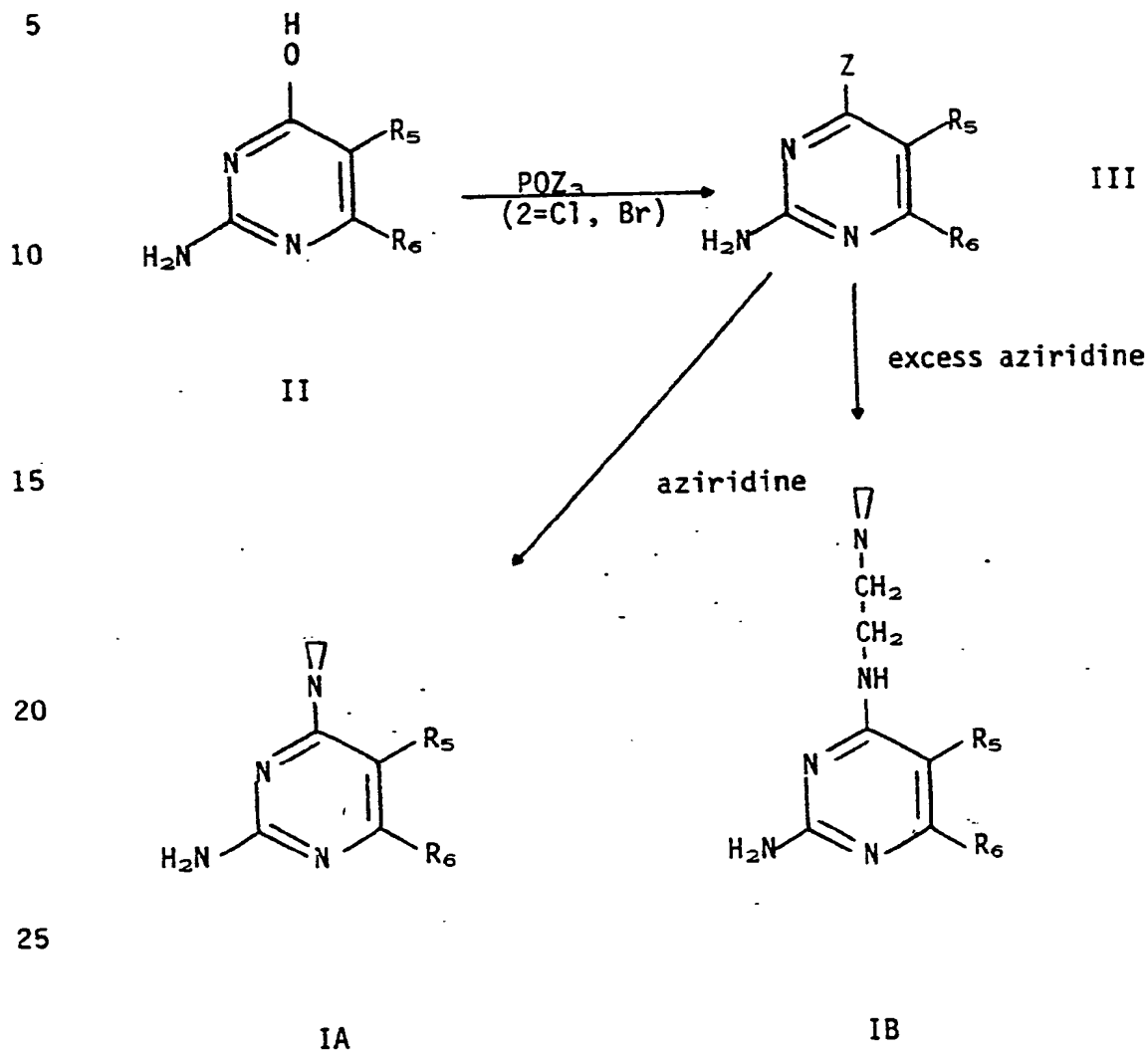


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-17-

CHART A



#184

TABLE I

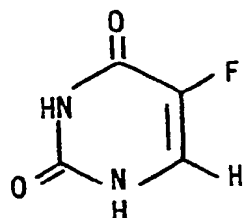
L1210

StructureID₅₀ μ g/mlID₉₀ μ g/ml

5

0.1

0.3

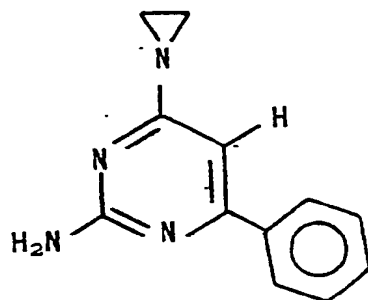


10

15

0.38

1.0

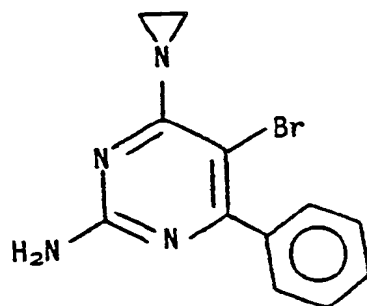


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1.2

3.2



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-19-

L1210

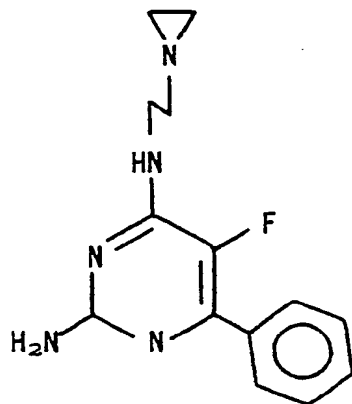
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5

0.78

2.1

10

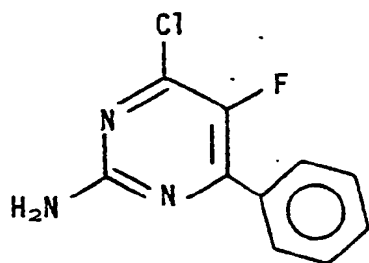


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0.18

0.55

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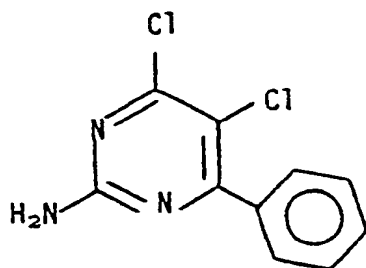


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0.91

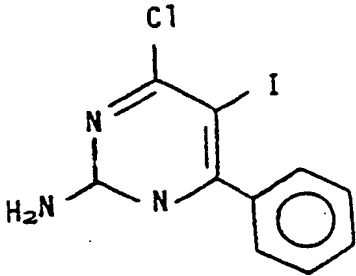
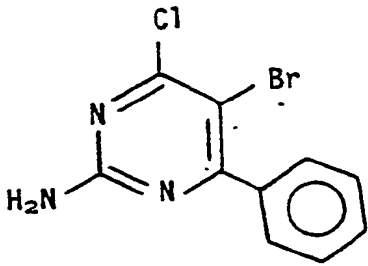
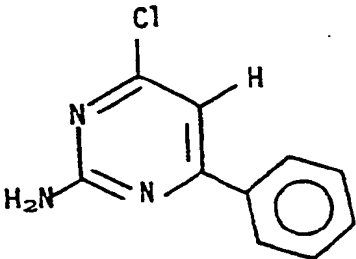
2.1

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-20-

<u>Structure</u>	<u>ID₅₀ μg/ml</u>	L1210	<u>ID₉₀ μg/ml</u>
5  <chem>Nc1nc(Cl)c(I)c(c1)c2ccccc2</chem>	1.8	3.9	
15  <chem>Nc1nc(Cl)c(Br)c(c1)c2ccccc2</chem>	0.64	1.6	
25  <chem>Nc1nc(Cl)c(c(c1)c2ccccc2)N</chem>	8.2	19.0	
35			

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TABLE II

	<u>Tumor</u>	<u>Dose^a</u>	<u>% ILS^b</u>	<u>Weight Change^c</u>
5	i.p.-P388	40	47	-3.8
		20	25	-0.7
		10	11	+2.1
		5	10	+1.8
10	i.p.-P388	40	26	-2.0
		20	17	+0.5
		10	11	+2.1
		5	14	+1.8
15	i.p.-L1210	40	24	-2.4
		20	9	+0.6
		10	0	+1.5
		5	0	+1.2
20	i.p.-B16	50	7	-3.0
		25	11	-0.5
		12.5	4	+0.3
		6.3	2	+1.2

^amg/kg/day, daily x 9, i.p., administered as a Klucel Suspension.

^b% increase in life span of treated compared to control animals.

^cg/mouse between days 1 and 5 after tumor inoculation.

The NCI-designated criteria of significant activity for synthetic agents in these 3 systems are: for P388, 20% ILS; L1210 and B16, 25% ILS.

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TABLE III

	<u>Test Organism</u>	<u>Assay Medium</u>	<u>Zone of Inhi- bition (mm)</u>
5	<u>E. coli</u>	B	0
	<u>S. schottmuelleri</u>	B	0
	<u>B. fragilis</u>	H	23
	<u>S. luteau</u>	C	0
	<u>E. coli</u>	E	0
	<u>S. pastorianus</u>	G	0
10	<u>P. vulgaris</u>	B	0
	<u>S. lutea +</u>	C	0
	<u>Ps. aeruginosa</u>	B	0
	<u>S. aureus</u>	B	0
	<u>Rhodopseudomonas spheroides</u>	F	18
	<u>K. pneumoniae</u>	A	0
	<u>B. subtilis</u>	A	21d
15	<u>S. pyogenes</u>	D	21
	<u>M. avium</u>	D	0

20

* A = Streptomycin Assay Agar (BBL)

B = Nutrient Agar (BBL)

C = Pen-Assay Seed Agar (BBL)

25 D = Brain Heart Infusion Agar (Difco)

E = Synthetic Medium (Mineral Salts - BBL)

F = Plate Count Medium (Difco)

G = Gray's Medium (Am. Type Culture Medium #855, AM. Type Culture
Catalog of Strains (I), 1982)

H = Schaedler Agar (Difco)

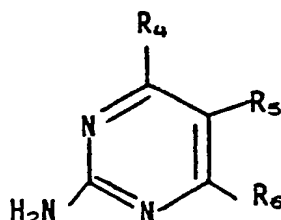
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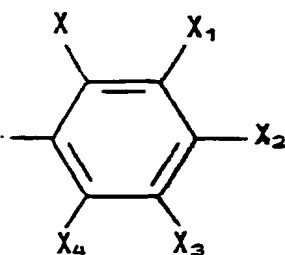
-23-

CLAIMS

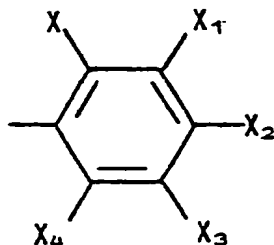
1. A compound of the formula



- 10 wherein R₄ is chloro, bromo, aziridyl or 2-(1-aziridyl)ethylamino;
 R₅ is hydrogen, fluoro, chloro, bromo, or iodo; and
 R₆ is a member selected from the group consisting of
 (a) phenyl,
 (b) a monosubstituted phenyl of the formula:



- wherein only one of the groups X, X₁, X₂, X₃ and X₄ is other than
 hydrogen and is fluoro, chloro, bromo, iodo, alkyl of from 1 to 5
 carbon atoms, inclusive, including isomeric forms, alkoxy of from 1 to
 25 5 carbon atoms, inclusive, including isomeric forms, nitro or dialkylamino
 of from 1 to 3 carbon atoms, inclusive, including isomeric forms; and
 (c) a disubstituted phenyl of the formula:



- wherein any two of X, X₁, X₂, X₃ and X₄ are not hydrogen and are the
 same or different and are fluoro, chloro, bromo, iodo, alkyl of from 1

-24-

to 5 carbon atoms, including isomeric forms, alkoxy of from 1 to 5 carbon atoms, inclusive isomeric forms, nitro or dialkylamino with the proviso that when R₄ is chloro and R₆ is phenyl, R₅ is not hydrogen of from 1 to 3 carbon atoms, inclusive, including isomeric forms, or where
 5 R₄ is chloro or bromo, a pharmacologically acceptable acid addition salt thereof.

2. A compound according to Claim 1, selected from the group consisting of:

10 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine;
 4-(1-aziridyl)-5-bromo-6-phenyl-2-pyrimidinamine;
 N'-[2-(1-aziridyl)ethyl]-5-fluoro-6-phenyl-2,4-pyrimidinediamine;

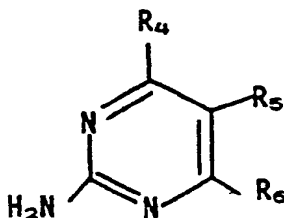
or

15 4-chloro-5-fluoro-6-phenyl-2-pyrimidinamine or a pharmacologically acceptable acid addition salt thereof.

3. A compound according to Claim 1, selected from the group consisting of 4,5-dichloro-6-phenyl-2-pyrimidinamine, 4-chloro-5-iodo-6-phenyl-2-pyrimidinamine, 4-chloro-5-bromo-6-phenyl-2-pyrimidinamine or a
 20 pharmacologically acceptable acid addition salt thereof.

4. A process for treating an animal or human hosting a neoplastic disease which comprises administration of an effective anti-neoplastic amount of a compound of the formula

25



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wherein R₄ is chloro, bromo aziridyl or 2-(1-aziridyl)ethylamine;

R₅ is hydrogen, fluoro, chloro, bromo, or iodo; and

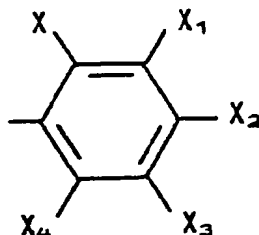
R₆ is a member selected from the group consisting of

35

(a) phenyl,

(b) a monosubstituted phenyl of the formula:

-25-



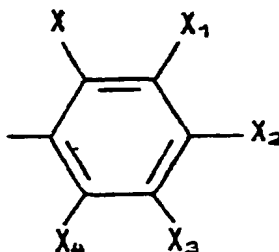
A

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wherein only one of the groups X, X₁, X₂, X₃ and X₄ is other than hydrogen and is fluoro, chloro, bromo, iodo, alkyl of from 1 to 5 carbon atoms, inclusive, including isomeric forms, alkoxy of from 1 to 5 carbon atoms, inclusive, including isomeric forms, nitro or dialkylamino of from 1 to 3 carbon atoms, inclusive, including isomeric forms; and

(c) a disubstituted phenyl of the formula:

15



wherein any two of X, X₁, X₂, X₃ and X₄ are not hydrogen and are the same or different and are fluoro, chloro, bromo, iodo, alkyl of from 1 to 5 carbon atoms, inclusive isomeric forms, nitro or dialkylamino of from 1 to 3 carbon atoms, inclusive, including isomeric forms, or when R₄ is bromo or chloro, a pharmacologically acceptable acid addition salt thereof; in combination with a pharmaceutical carrier.

5. A process according to Claim 4 where the compound is selected from the group consisting of:

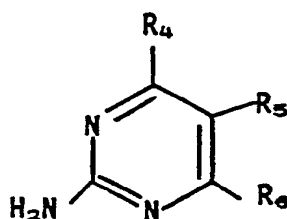
30 4-(1-aziridyl)-6-phenyl-2-pyrimidinamine;
4-(1-aziridyl)-5-bromo-6-phenyl-2-pyrimidinamine;
N'-[2-(1-aziridyl)ethyl]-5-fluoro-6-phenyl-2,4-pyrimidinediamine;
or

35 4-chloro-5-fluoro-6-phenyl-2-pyrimidine or a pharmacologically acceptable acid addition salt thereof.

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6. A process according to Claim 4 where the compound is selected from the group consisting of 4,5-dichloro-6-phenyl-2-pyrimidinamine, 4-chloro-5-iodo-6-phenyl-2-pyrimidinamine, 4-chloro-5-bromo-6-phenyl-2-pyrimidinamine or a pharmacologically acceptable acid addition salt thereof.

7. A pharmaceutical composition for treating neoplastic diseases comprising an effective amount of a compound of the formula



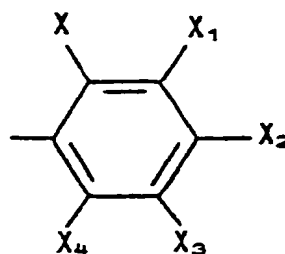
wherein R_4 is chloro, bromo aziridyl or 2-(1-aziridyl)ethylamine;

R_5 is hydrogen, fluoro, chloro, bromo, or iodo; and

R_6 is a member selected from the group consisting of

(a) phenyl,

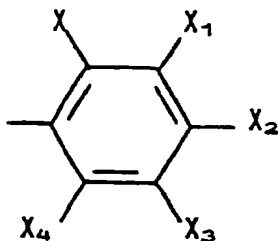
(b) a monosubstituted phenyl of the formula:



wherein only one of the groups X, X_1 , X_2 , X_3 and X_4 is other than hydrogen and is fluoro, chloro, bromo, iodo, alkyl of from 1 to 5 carbon atoms, inclusive, including isomeric forms, alkoxy of from 1 to 5 carbon atoms, inclusive, including isomeric forms, nitro or dialkylamino of from 1 to 3 carbon atoms, inclusive, including isomeric forms; and

(c) a disubstituted phenyl of the formula:

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wherein any two of X, X₁, X₂, X₃ and X₄ are not hydrogen and are the same or different and are fluoro, chloro, bromo, iodo, alkyl of from 1 to 5 carbon atoms, including isomeric forms, alkoxy of from 1 to 5 carbon atoms, inclusive isomeric forms, nitro or dialkylamino of from 1 to 3 carbon atoms, inclusive, including isomeric forms, or when R₄ is bromo or chloro, a pharmacologically acceptable acid addition salt thereof; and a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/US-86/00074**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : C 07 D 239/42; C 07 D 403/04; C 07 D 403/12; A 61 K 31/505								
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="vertical-align: top; padding: 5px;">IPC⁴</td> <td style="padding: 5px;">C 07 D 239/00 C 07 D 403/00</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	IPC ⁴	C 07 D 239/00 C 07 D 403/00		
Classification System	Classification Symbols							
IPC ⁴	C 07 D 239/00 C 07 D 403/00							
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category ¹⁰</th> <th style="width: 70%; border-bottom: 1px solid black;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; border-bottom: 1px solid black;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="vertical-align: top; text-align: center; padding: 5px;">X</td> <td style="padding: 5px;">US, A, 3412094 (K.J. RORIG et al.) 19 November 1968, see columns 1,5,6; example 1 -----</td> <td style="vertical-align: top; text-align: center; padding: 5px;">1,7</td> </tr> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 3412094 (K.J. RORIG et al.) 19 November 1968, see columns 1,5,6; example 1 -----	1,7
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³						
X	US, A, 3412094 (K.J. RORIG et al.) 19 November 1968, see columns 1,5,6; example 1 -----	1,7						
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>								
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of the Actual Completion of the International Search 16th April 1986</td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">Date of Mailing of this International Search Report 30 MAI 1986</td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">International Searching Authority EUROPEAN PATENT OFFICE</td> <td style="border-bottom: 1px solid black; padding: 5px;">Signature of Authorized Officer M. VAN MOL </td> </tr> </table>			Date of the Actual Completion of the International Search 16th April 1986	Date of Mailing of this International Search Report 30 MAI 1986	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. VAN MOL		
Date of the Actual Completion of the International Search 16th April 1986	Date of Mailing of this International Search Report 30 MAI 1986							
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. VAN MOL							

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO.

PCT/US 86/00074 (SA-- 11994)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/04/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3412094		None	

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82

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